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Investigation of the cyclization of dihydroisotryptamine

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INVESTIGATION OF THE CYCLIZATION OF DIHYDROISOTRYPTAMINE

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S U M M A R Y

Dihydroisotryptamine was prepared, as its crystalline hydrochloride, in sufficient quantities to enable investigation of its general properties and the possibilities of its successful cyclization to tricyclic structures which are isomeric with corresponding tryptamine derivatives present e.g. among harmala alkaloids.

During the course of the research programme two different methods were investigated:

1. Ringclosure reactions of the newly prepared acetyl and benzoyl derivatives of dihydroisotryptamine according to the Bischler-Napieralski reaction, an approach which, in all its modifications, proved to be unsuccessful and

2. Ringclosure reactions of Schiff-bases formed between appropriate aldehydes and dihydroisotryptamine based on the Pictet-Spengler reaction. The method developed this way enabled the successful preparation of a tricyclic ring-system in the form of dihydroiso-indolo-[1,2-c]hexahydropyrimidine derivatives. The formation of this new structure was achieved in one step i.e. without the necessity of isolating the intermediate Schiff-base.

I N T R O D U C T I O N

RING CLOSURE REACTIONS

Ring closure reactions of ethylamino side-chain of β-aryl substituted α-amino acids to, usually, six-membered ring systems (heteroaromatic or heteroalicyclic) are well known and are discussed in detail in the chemical literature. The most important methods employed for the formation of these new rings are:

(a) the Pictet-Spengler cyclization reaction and

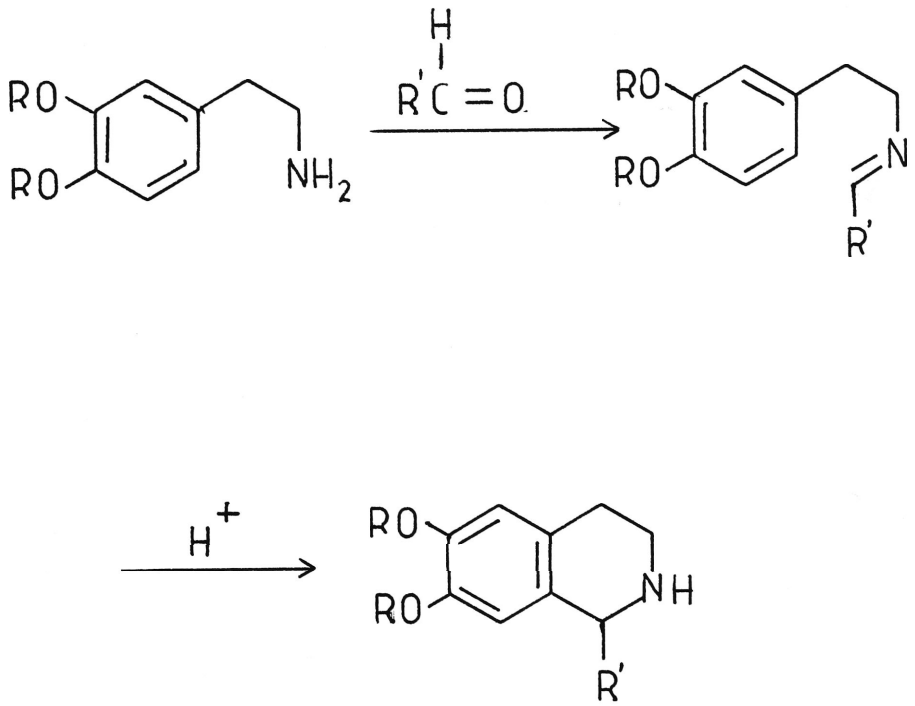
(b) the Bischler-Napieralski reaction.

These reactions deal mainly with the synthesis of pyridine ring systems including their fully or partially hydrogenated derivatives, e.g. isoquinolines, tetrahydroisoquinolines, β-carbolines and tetrahydrocarbolines.

A. The Pictet-Spengler Cyclization Reaction.

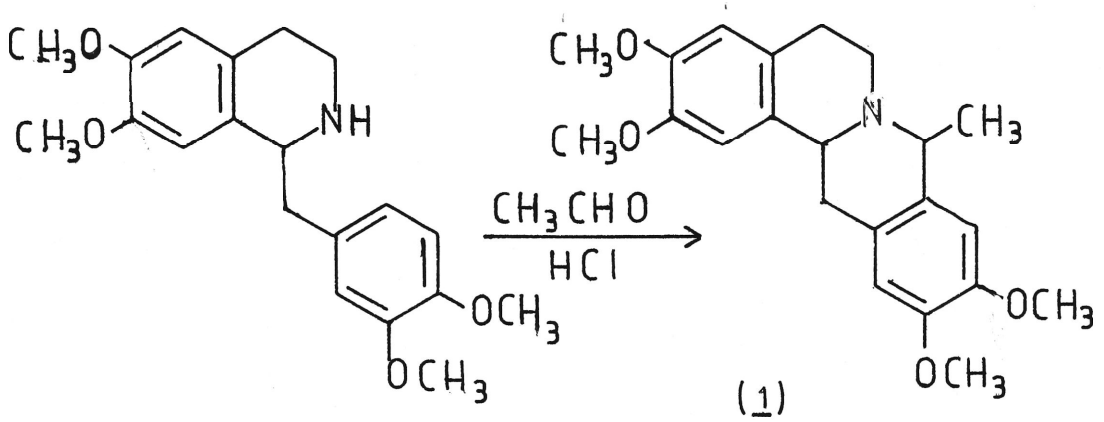
In its simplest form the reaction consists of condensation of β-arylethylamine with a carbonyl compound (either aldehydes or ketones) to yield pyridine like structures most often in a reduced form.

Pictet and Spengler[1] were the first to realise that β-phenethylamine reacts with methanal in concentrated hydrochloric acid to yield 1,2,3,4-tetrahydroisoquinoline. This reaction was extended by Decker,[2] employing substituted phenethylamines with various aldehydes as shown below:

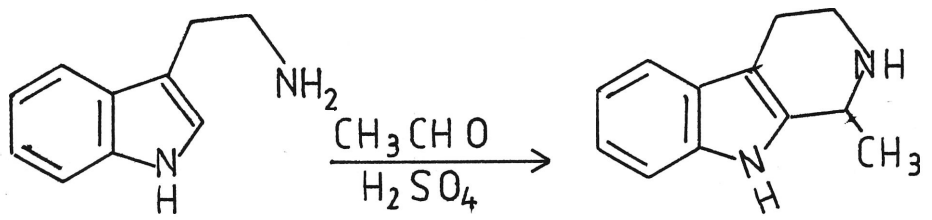


The reaction was carried out in two steps in which the intermediate, azomethine was cyclized in the presence of an acid.

Since its introduction, the Pictet-Spengler reaction has been successfully applied to the syntheses of other ring systems, notably to partly saturated dibenzoquinolizines and 2-carbolines. Typical examples are the preparation of 2,3,10,11-tetramethoxy-8-methyl-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine[3] (1), and 1-methyl-1,2,3,4-tetrahydro-2-carboline[4] (2).



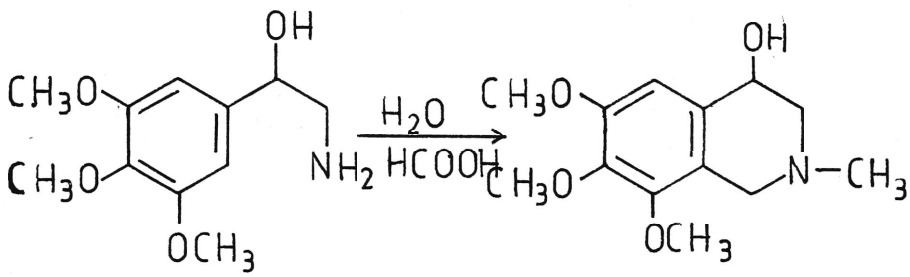
(1)



(2)

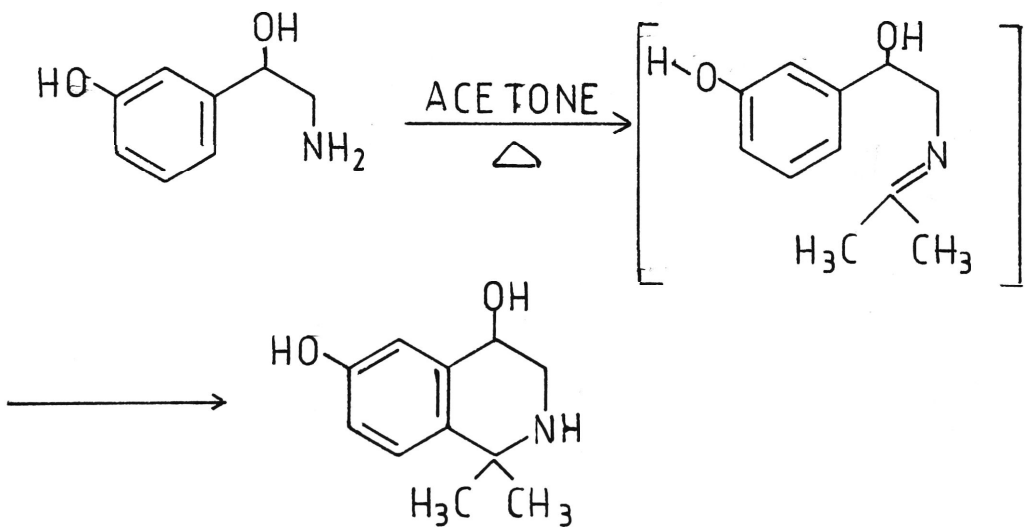
Schopf and Bayerle[5] carried out the Pictet-Spengler reaction under 'physiological' condition i.e. temperature, concentration and acidity of the reaction medium was comparable to that which might exist in plants, to explain the origin of isoquinoline and β-carboline alkaloids found in plants. For example, synthesis of (2) can also be achieved at physiological conditions of pH5 at 25°C in 70% yield after 3 days.[6] Under similar conditions dopamine and acetaldehyde condensed to give

83% O-norsalsoline[5]. Condensation of 3,4-dihydroxyphenylethylamine with homopiperonal at pH6 and 25°C yielded 84% of 1-piperonyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline[7]. Under conditions similar to those described above, amino alcohol (3) yields with formaldehyde and formic acid not only the N-methylated compound but resulted also in a Pictet-Spengler cyclization to 4-hydroxytetrahydroisoquinoline[8].

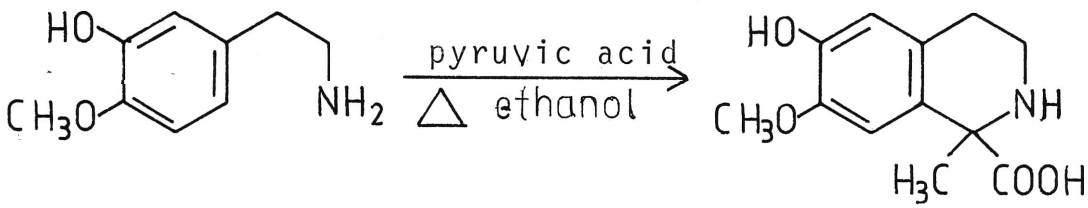


(3)

Certain other aromatics activated by phenolic functional groups present in <u>para</u> position to the cyclization site also follow the Pictet-Spengler type reaction. Such phenolic cyclization is evident in the synthesis of 4,6-dihydroxy-1,1-dimethyltetrahydroisoquinoline, when 3-hydroxyphenyl(α-hydroxy)ethylamine is heated in acetone[9].

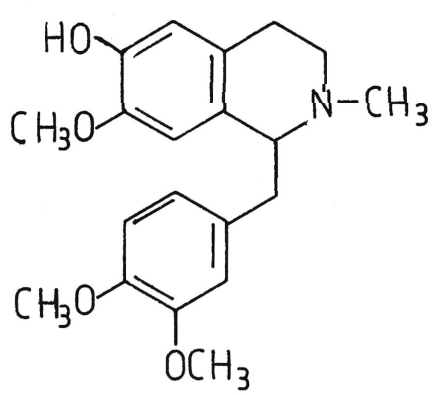


The condensation of phenethylamine with pyruvic acid when refluxed in ethanol to give the amino-acid[9] (4) represents a similar cyclization reaction.



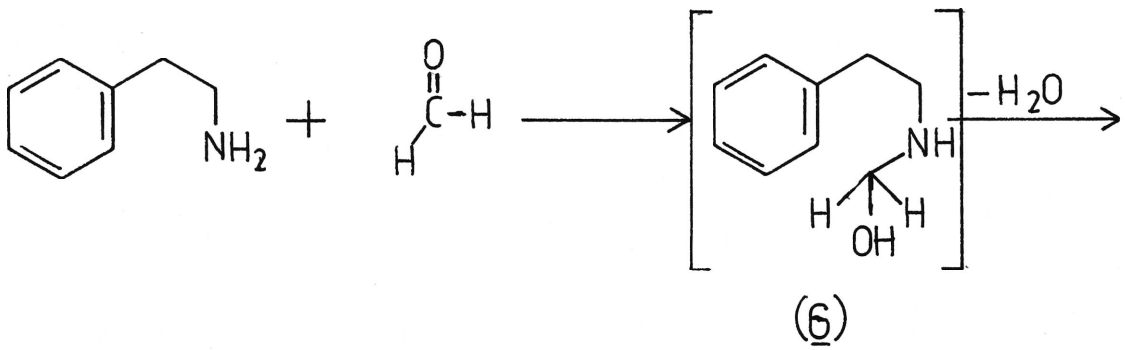
(4)

Although the reaction of pyruvic acid is much slower than those of aldehydes, such condensation reaction works well when a free phenolic function is available para to the cyclization site. Condensation will in fact take place even without the use of an acid catalyst to afford cyclization. Pseudolaudanine (5) was e.g. obtained from homoisovanillylamine and homoveratraldehyde in ethanol at room temperature if the initial cyclized product was N-methylated according to the procedure of Eschweiler-Clarke.[10]

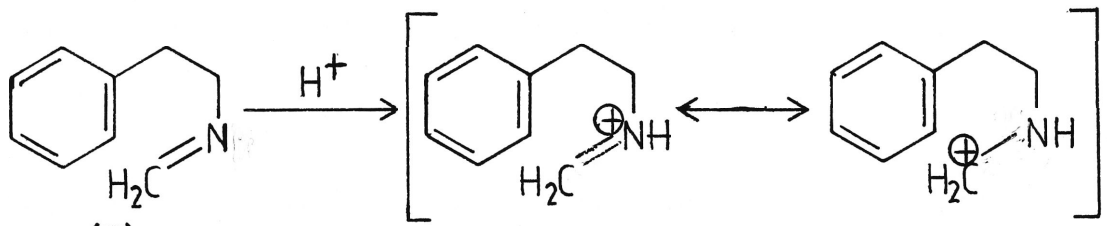


(5)

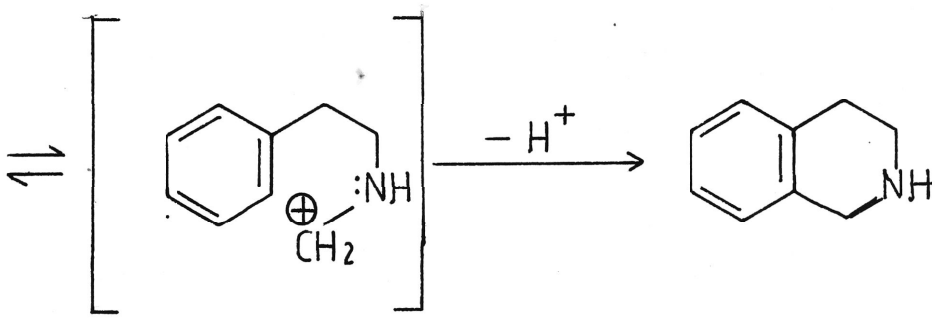
The reaction mechanism of this condensation and ring closure between a β-phenylethylamine derivative and an aldehyde is generally accepted to commence with Schiff-base formation between them (c.f. 7) followed by an electrophilic attack to substitute the aromatic ring in the ortho position as shown below.



(6)

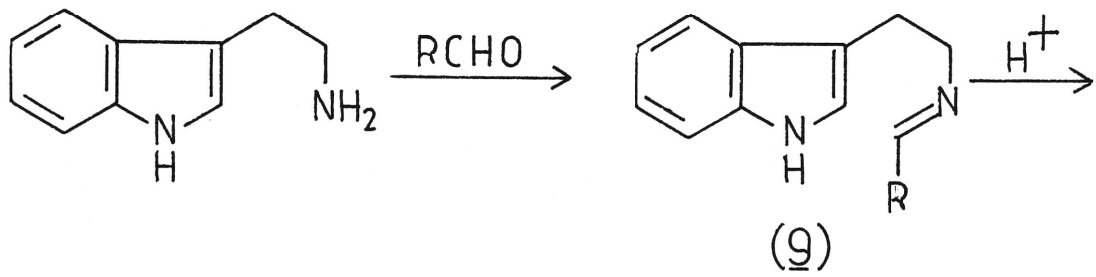


(7) (8)

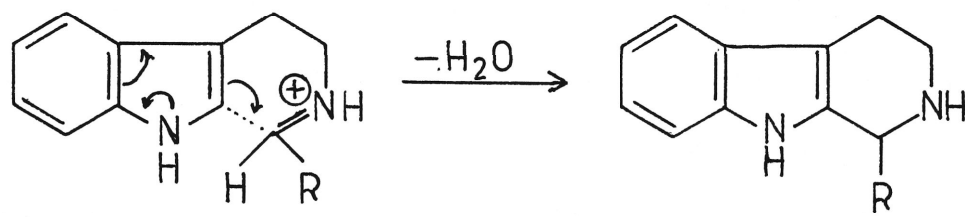


The Schiff base intermediate (i.e. the imine (7)) has been identified and also isolated from many reaction mixtures. It was also shown to yield the final product by acid-catalyzed cyclization. If, however, the amine component is not a primary but a secondary amine then the reaction intermediate must be hydroxymethyl derivative (e.g. 6) which cannot lose water to form (7). In this case Schiff-base formation is by-passed and (8) is formed directly under the influence of the catalyzing acid. The tendency of some Pictet-Spengler reactions to succeed even at pH7 (i.e. in non-acidic medium) can be readily explained by the capability of the aliphatic amines used in this reaction to form ammonium ions in presence of water only. Obviously pyruvic acid, which possesses no β-hydrogenation, cannot directly undergo the Pictet-Spengler cyclization reaction. However, those derivatives of pyruvic acid which can enolize will cyclize[11].

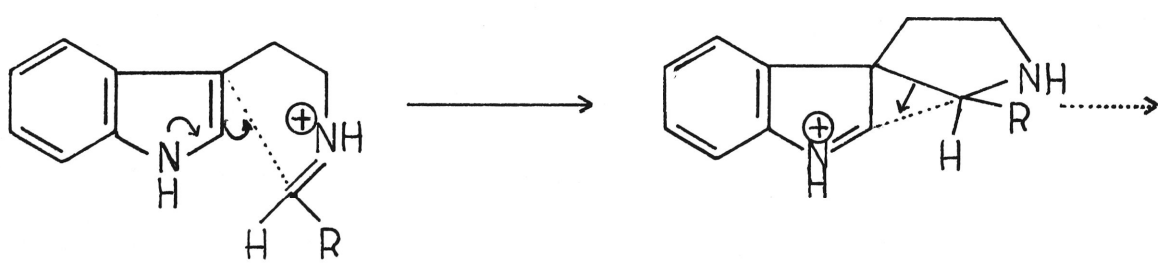
Tryptamines condense with aldehydes to give tetra-hydro-β-carbolines. This cyclization also suggests the initial formation of Schiff bases e.g. (9) which is then followed by electrophilic attack at C-2 of the indole ring to form the tricyclic compounds[12].

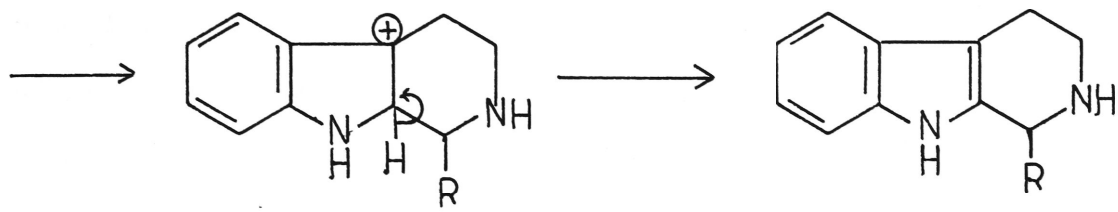


(9)

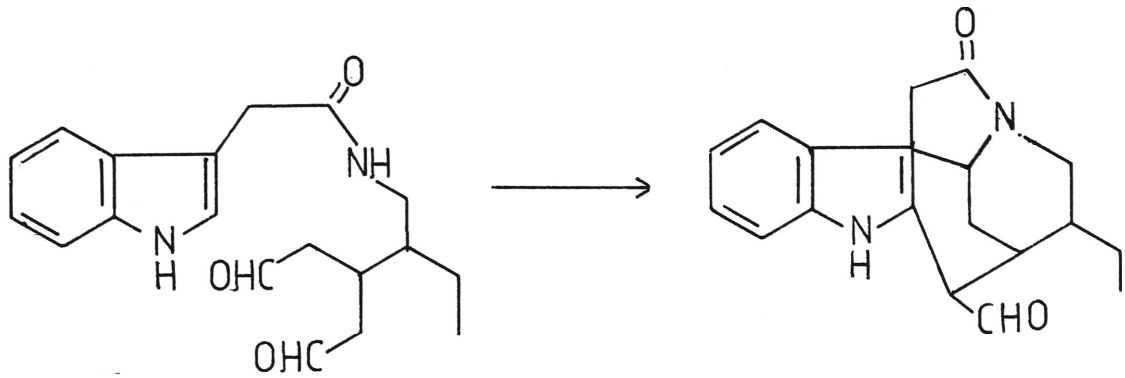


Jackson and Smith[13] suggested that Schiff bases which formed from tryptamine derivatives follow the same pattern of electrophilic substitution as simple 3-alkylindoles. This means that the 'cyclizing' electrophilic substitution initially proceeds in the 3-position forming indolenine derivatives which rearrange to β-carboline derivatives.





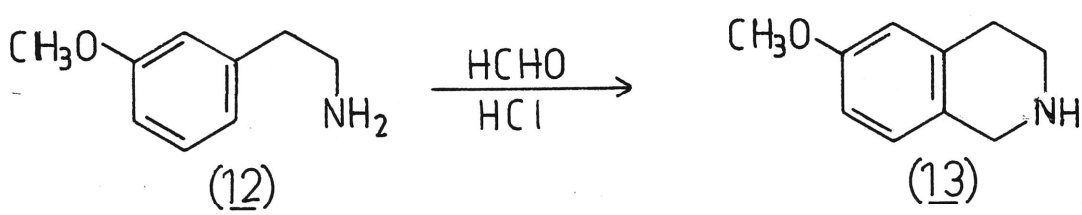
Recent intramolecular cyclizations of this type[14] gave support to the claim that the above reactions actually proceed via indolenine intermediate e.g. that of 3'-indolyl-ethanoyl-2-cyclopentenylbutyl-1-amine, gave indirect evidence for and support to the claim that above reactions actually proceed via indolenine intermediates. The cyclization[15] of (10) to (11) represents another suitable example.



(10) (11)

One of the intermediate steps in Woodward's synthesis of strychnine[16] also provides an example of cyclization occurring at the 3-position when C-2 position is blocked.

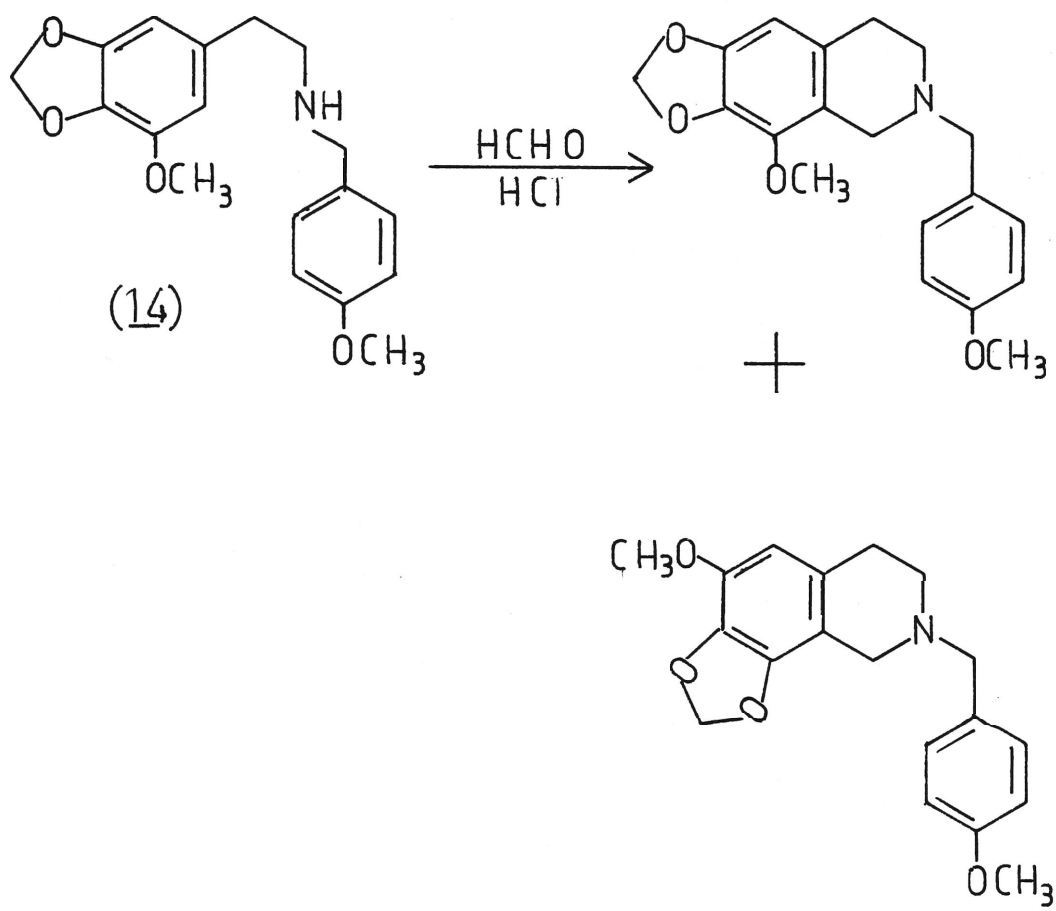
As the Pictet-Spengler cyclization and also the Bischler-Napieralski reaction[17] as will be shown later proceed via electrophilic aromatic substitution, it is obvious that the electron density on the to-be-substituted carbon must be a determining influence. It will be determined which of the two unsubstituted ortho-positions of the aromatic ring will be the preferred position for cyclization. As a general expectation the ortho position which is para to the electron-donating substituent will be preferred as shown by the following example. Condensation of 3-methoxyphenethylamine (12) with formaldehyde yields only the 6-methoxytetrahydroisoquinoline (13) and not the 8-methoxy derivative which could have resulted from the cyclization in the alternative ortho position[18].



(12) (13)

It was also reported - and this gives additional support to the above claim - that cyclization of 3,4-dialkoxy-β-phenylethylamine with formaldehyde, under conditions similar to those described, yields only the 6,7-dialkoxy- (and not the 7,8-dialkoxy-) -1,2,3,4-tetrahydroisoquinoline[19]. If both ortho-positions are

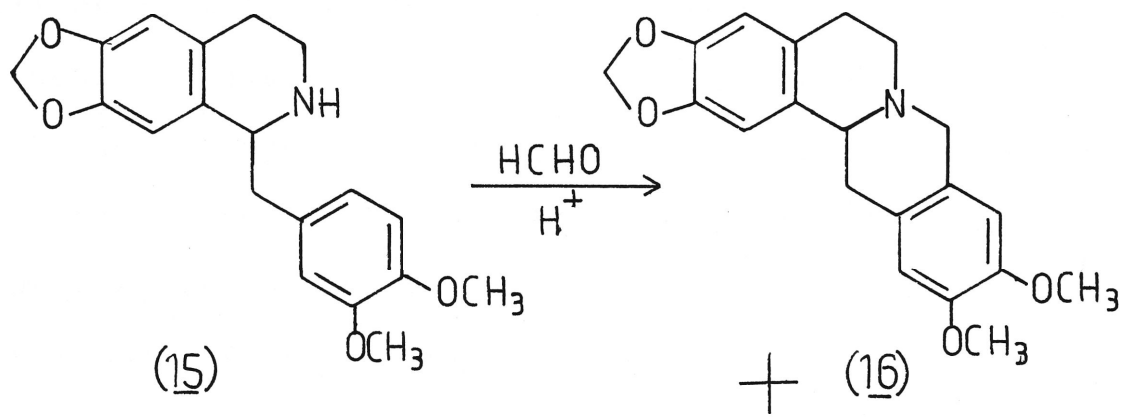
activated (by e.g. a methoxy - and a methylenedioxy - group) such as in (14) then a mixture of both compounds are formed as shown by the cyclization, with formaldehyde, of N-(3-methoxybenzyl)homomyristicylamine (14).



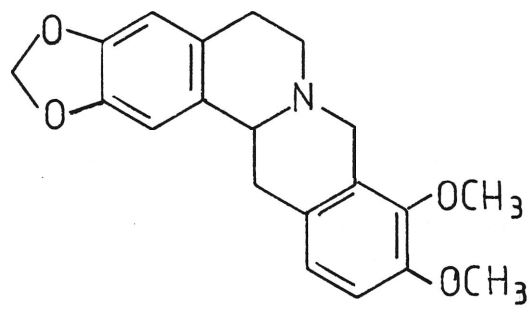
(14)

That the above examples are significant and represent the preference given to the position para to an electron-donating substituent is further underlined by the cyclization[20,21] again with formaldehyde, of l-veratryl-nor-hydrohydrastine, (15), nearly exclusively to

tetrahydropseudoberberine (16), producing the other minor isomer, canadine, only in very small amounts.

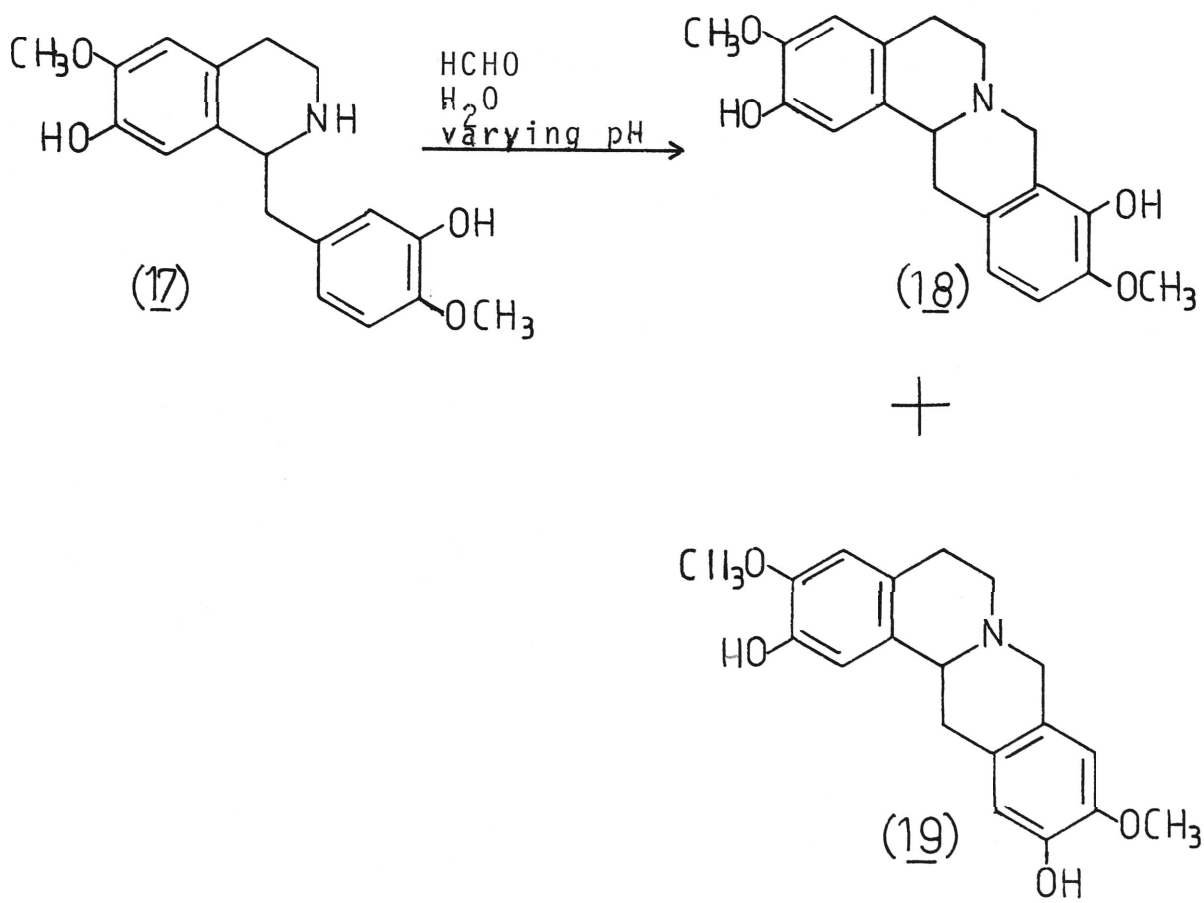


(15) + (16)



In order to explore the general applicability of the above results Spath[22,23] replaced the alkoxy substituents by the more active hydroxyl groups and showed that the same rule does not usually apply, i.e. ring-closure proceeds *via* both *ortho* positions, and a mixture of 9,10-dihydroxy- and 10,11-dihydroxy derivatives are formed. If however the ring-closure reaction was carried out under

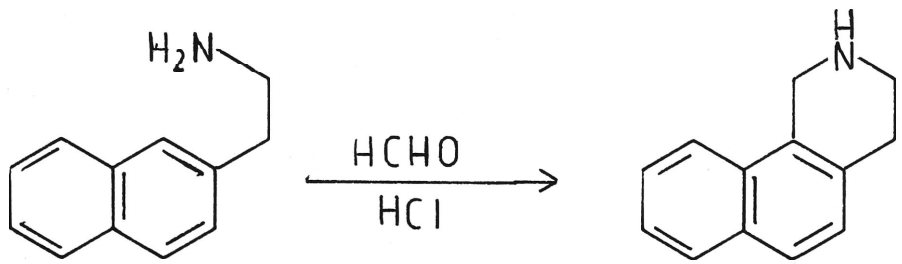
physiological conditions[22], the 9,10-dihydroxy- product was formed in 80% yield. Whaley[17] explained this apparently contradictory phenomenon by stating that the presence of free hydroxyl groups in the benzyl residue activates both ortho positions to such an extent that instantaneous cyclization occurs via whichever ortho position is made available by the random oscillation of the benzyl group. But, in case e.g. norreticuline (17) which has one hydroxyl and one methoxyl substituent on the benzyl ring of the tetrahydrobenzylisoquinoline structure, two products, viz. scoulerine (18) and coreximine (19) are formed.



In fact it has been shown[24,25] that the pH of the reaction medium determines, apparently, the relative quantities of the two compounds formed. At pH6.3, the ratio of scoulerine to coreximine is 2 to 1 while at the neutral pH coreximine is the only product formed.[24]

It is interesting to note that, initially, it was tacitly assumed that condensation of m-hydroxyphenylethylamines with pyruvic acid produced only 6-hydroxy-1,2,3,4-tetrahydroisoquinoline derivatives without even considering the possibility of ring-closure in the other direction[26]. This assumption was however quickly discontinued when it was shown[27,28] that anhalamine is 6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline.

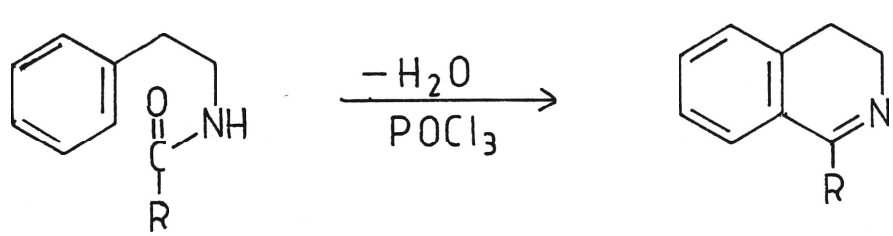
Similar results were obtained in case of ring-closure reactions with aminoethylnaphthalenes. Condensation of β-(2-naphthyl)ethylamine with formaldehyde yielded only 1,2,3,4-tetrahydro-7,8-benzisoquinoline[29]. This was explained by the higher electron density at the α-position of the naphthalene ring compared to that at the β-position. This finding was underlined by the observation[29] that β-(2-naphthalenyl) ethylamine could not be cyclized under the conditions used above.



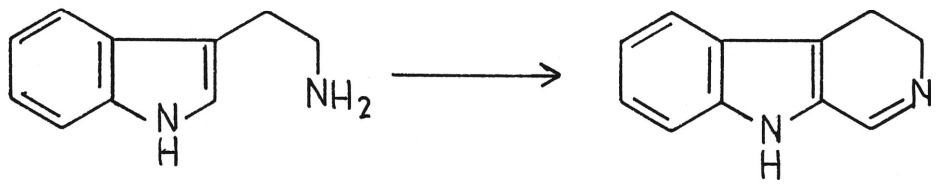
An attempt to cyclize 1-aminomethyl-2-methoxynaphthalene in the <u>peri</u> position was, as expected, also unsuccessful[30].

B. <u>The Bischler-Napieralski Reaction</u>.

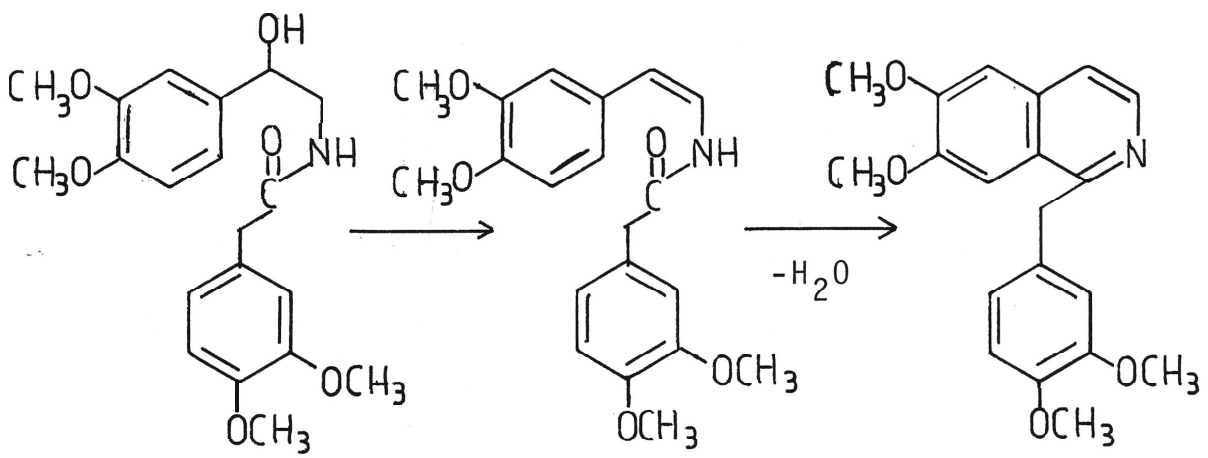
Cyclization of N-(β-arylethyl)amides of carboxylic acids to the corresponding 3,4-dihydroisoquinoline derivatives is carried out by the Bischler-Napieralski reaction in presence of acid catalysts e.g. P_2O_5, $POCl_3$, PCl_5, $ZnCl_2$, $AlCl_3$ or SO_2Cl_2.[31,32,33,34]



Similarly, amide derivatives of tryptamines also cyclize to 3,4-dihydro-β-carbolines .

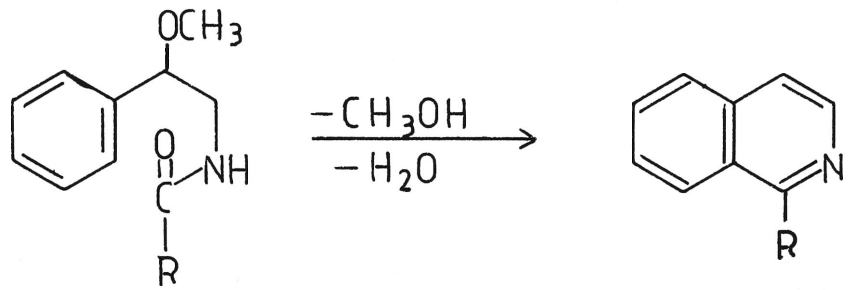


If the cyclization is carried out under cyclodehydrating conditions[34,36] then isoquinolines, instead of their dihydro-compounds, are formed, e.g. in the case of papaverine[34] (20) synthesis. The reaction is activated by irradiation with ultraviolet light,[37,38,39,40,41] and proceeds by dehydration of the acylated ethylamino side-chain, thereby forming a double bond, followed by cyclization.

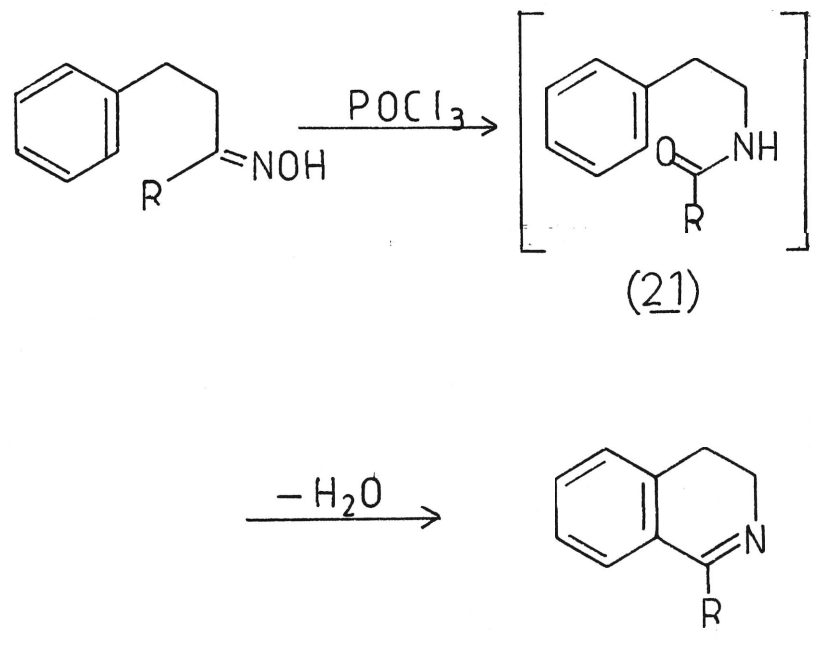


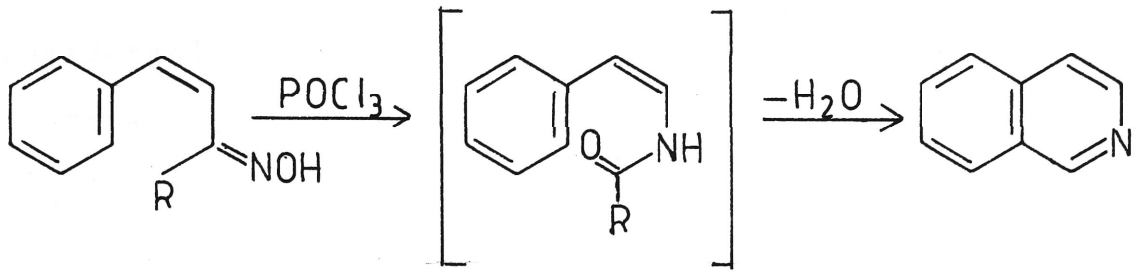
(20)

In addition to the loss of water from the above acylated hydroxyethyl amine derivatives the corresponding alkoxy ethylamine side-chains can (instead of water) lose an alcohol molecule to form isoquinoline derivatives[42,43].



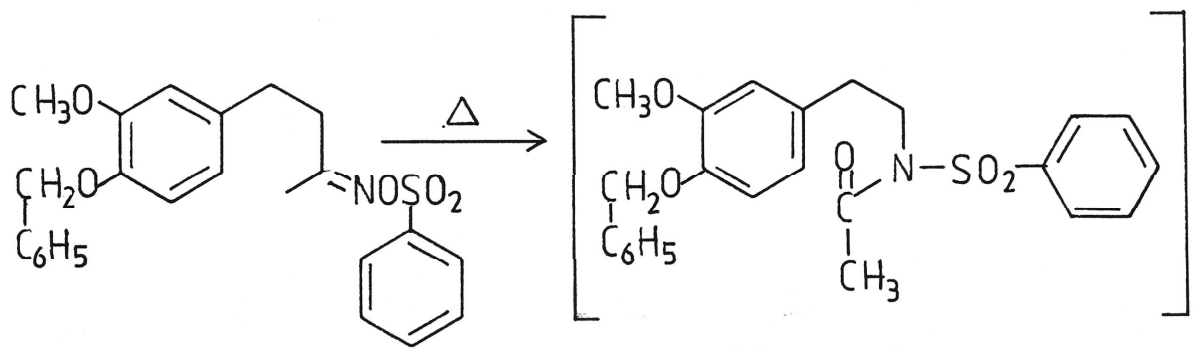
N-acyl-2-phenylethylamines (21)[44] and N-acylstyrylamine[45] (22), prepared by Beckmann rearrangement[46] from the appropriate oximes, also cyclize to 3,4-dihydroisoquinolines and isoquinolines respectively by Bischler-Napieralski reaction:

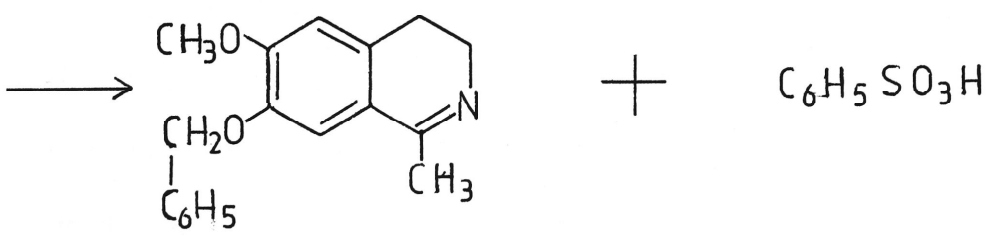




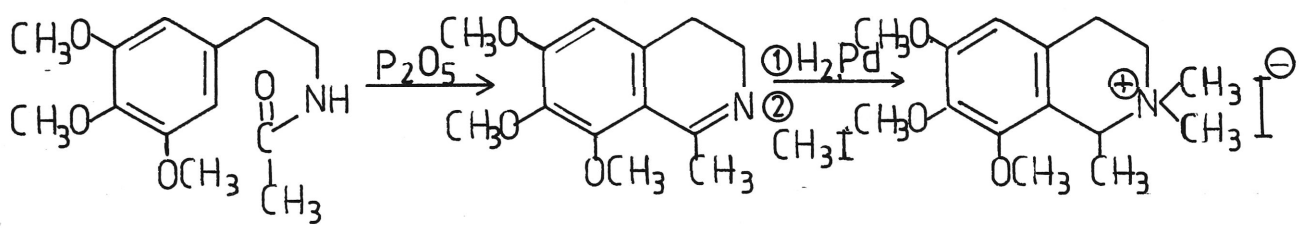
(22)

Benzenesulphonyl esters, which are excellent leaving groups, of this type of oximes tend to cyclize without the presence of dehydrating or oxidizing agents requiring only gentle heating for the transformation[47].



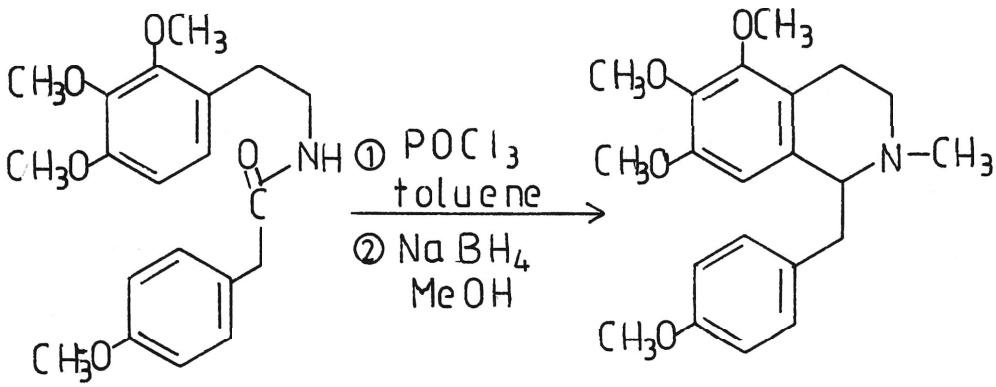


The reaction conditions employed critically influence the yield of the final product, which improves considerably if low temperatures and mild condensing agents are used. Under these milder conditions more complicated isoquinoline derivatives, e.g. benzoquinolizines and phenanthridines could also be synthesized[48]. As could be expected these amides which have an electron-releasing substituent on the aromatic ring cyclize more readily than those with no substitution, while presence of electron withdrawing substituents on the aromatic ring hinder the reaction. The facilitation of the reaction in this way is well illustrated by the ready cyclization of N-acetyl-3,4,5-trimethoxy-phenylethylamine to 3,4-dihydroisoquinoline derivative, which on methylation with methyliodide, gave O-methyl-pellotine[49].

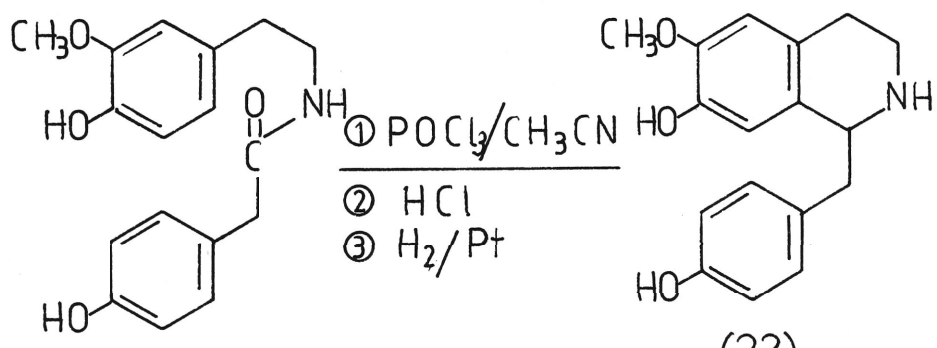


The Bischler-Napieralski reaction is the most commonly used method for the preparation of 1-benzylisoquinoline derivatives, whether they are fully aromatic or containing partially hydrogenated pyridine rings in their molecules. Most of these compounds usually possess two or three oxygenated substituents on the benzene ring portion

of the isoquinoline moiety, while the aromatic portion of the benzyl ring carries one or at most two such substituents. This is illustrated by the synthesis, via this reaction of takatonine and tetrahydrotakatonine[50].

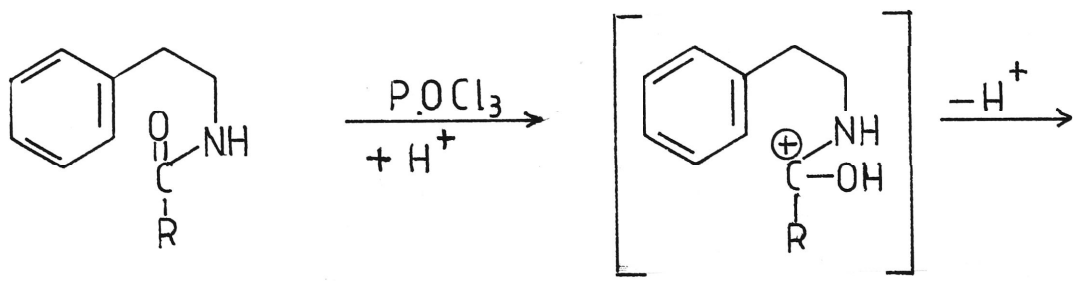


The use of acetonitrile as solvent promotes Bischler-Napieralski cyclization of the amide. Coclaurine (23) for instance was synthesized in over 60% yield in acetonitrile solution,[51] while a similar cyclization attempt with P_2O_5 in toluene gave much lower yield[52].



(23)

The mechanism of the reaction involves an intramolecular electrophilic attack by the carbonium ion e.g. (24), formed by protonation on the double bond of the aromatic ring in the same molecule (in one of the two ortho-positions) with subsequent elimination of a mole of water, followed by cyclization to 3,4-dihydroisoquinoline derivatives e.g. (25). This mechanism is, of course, in agreement with the promotion of cyclization by the presence of electron-releasing substituents in the aromatic portion of the molecule, discussed earlier.



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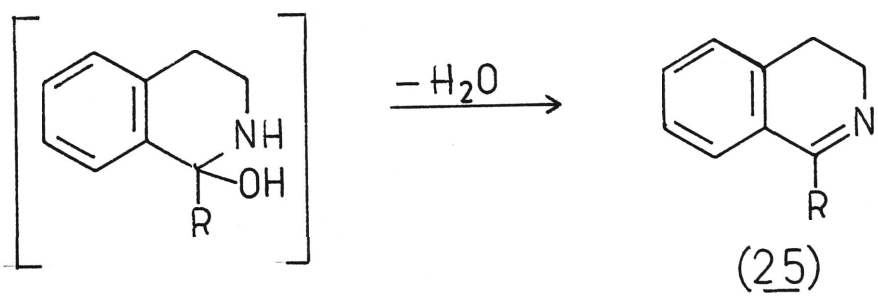
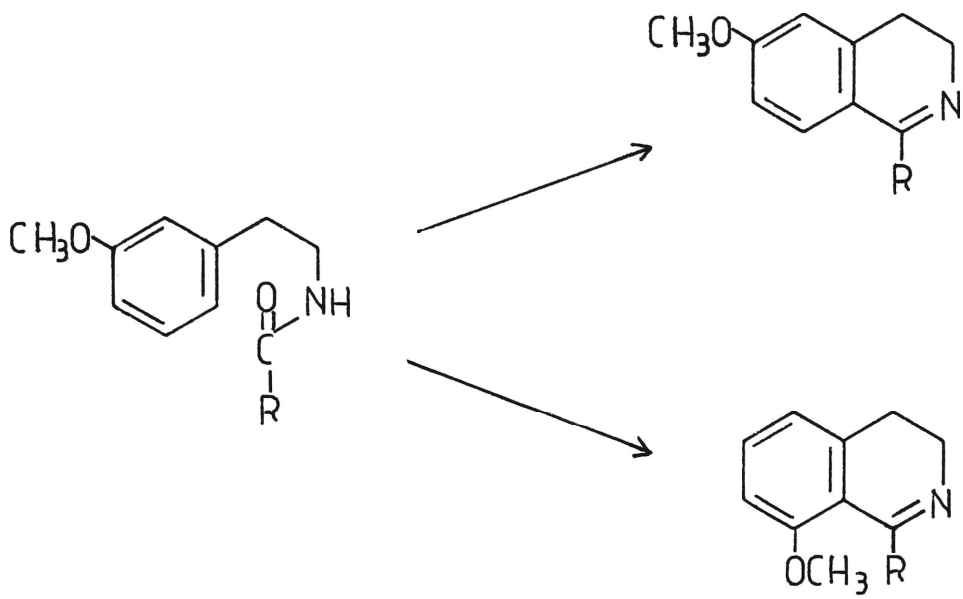
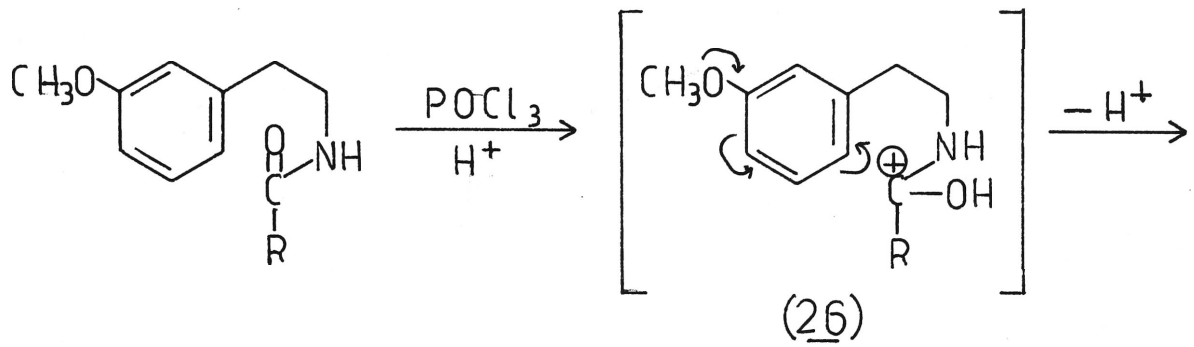


(25)

Cyclization of N-acyl-β-3-methoxyphenylethylamine may lead to either a 6-methoxy or an 8-methoxy-3,4-dihydroisoquinoline, depending on the direction of ring closure as shown.



When the position, para to the methoxy group is free, it invariably becomes the point of ring closure, leading to a 6-methoxyisoquinoline derivative. This fact is the result of an electrophilic attack on the aromatic ring by the same, but substituted, carbonium ion (26).



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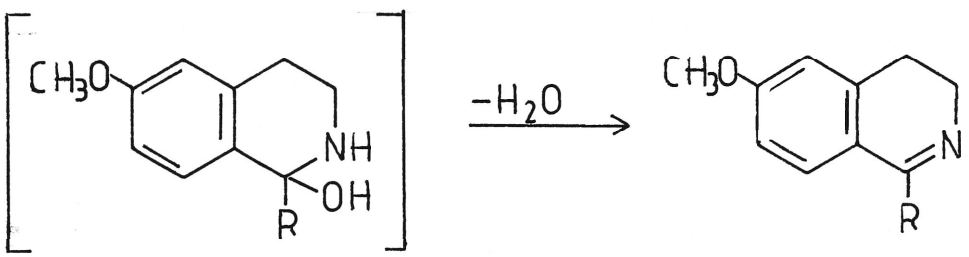
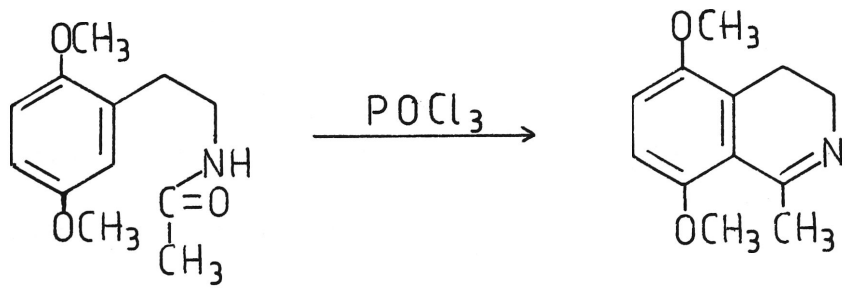
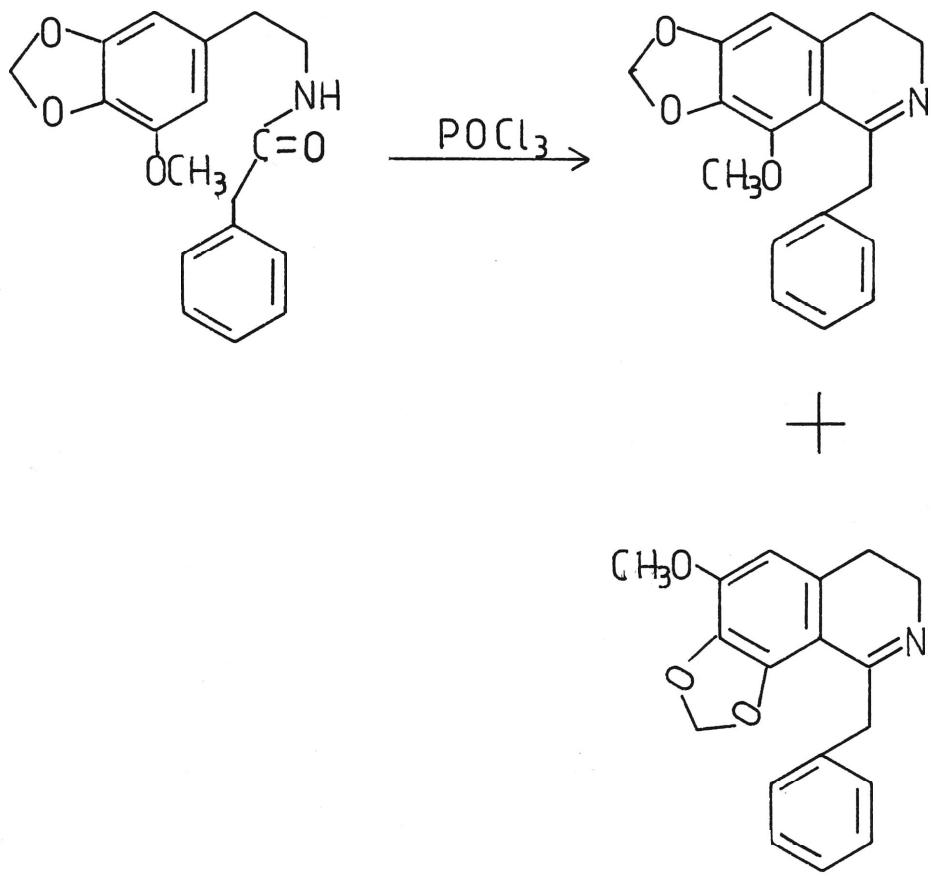


Where the para position is blocked as in N-acetyl-2,5-dimethoxy-β-phenethylamine (27) is readily converted to the 1-methyl-5,8-dimethoxy-3,4-dihydroisoquinoline[53].

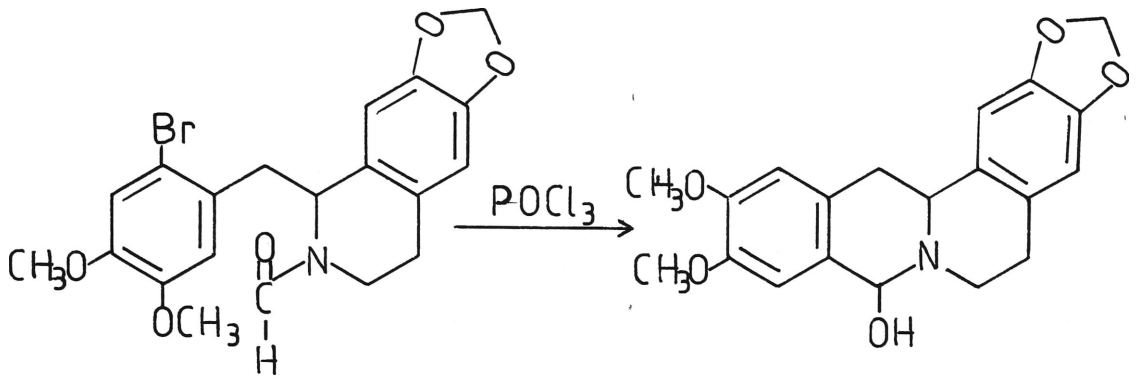


(27)

If both positions are activated to a similar degree, a mixture of products is obtained as in the cyclization of N-phenylacetylhomomyristicylamine to give 1-benzyl-8-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline[54].



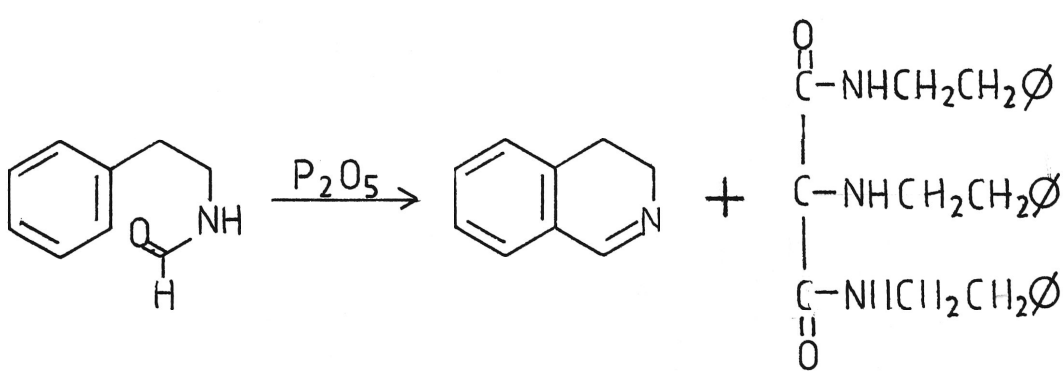
In the synthesis of cavidine (29) which is similar to berberine, the appropriate formamide derivative (28) was heated with phosphorus oxychloride. The product is a bromine-free cavidine rather than the expected bromodihydroberberine[55].



(28) (29)

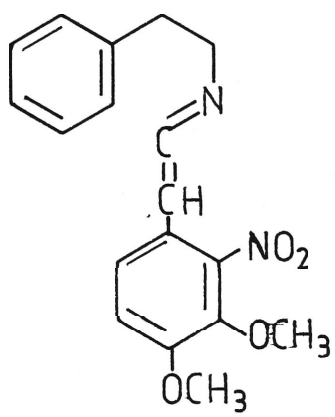
This ring-closure reaction shows the reaction's remarkable selectivity. The halogen substituent in <u>para</u> position of the aromatic ring is removed to make the preferred electron-rich position available for the electrophilic substitution reaction required for ring-closure.

However, not all Bischler-Napieralski reactions give cyclized products. The use of drastic cyclizing conditions may result in the production of tars (from the starting amides) which are not cyclized. Occasionally, side reactions have also been recorded. For example treatment of N-formyl-β-phenethylamine with phosphorus pentoxide yielded mostly aminomalondiamide[56] and only small amount of 3,4-dihydro-isoquinoline.



Cyclization of <u>m</u>- and <u>p</u>-nitrobenzyl derivatives of unactivated β-phenethylamines gave considerable proportions of the corresponding nitrobenzonitriles as by-products.[57] This reaction may be attributed to the resistance of the amides to cyclodehydration. Unactivated 2-nitrohomo-veratronyl-β-phenethylamine derivatives have

been found to undergo cyclodehydration in $POCl_3$ to give the corresponding products formulated as vinylideneamines (30, 31)[58,59,60] and as acetylene derivatives[61] (32).



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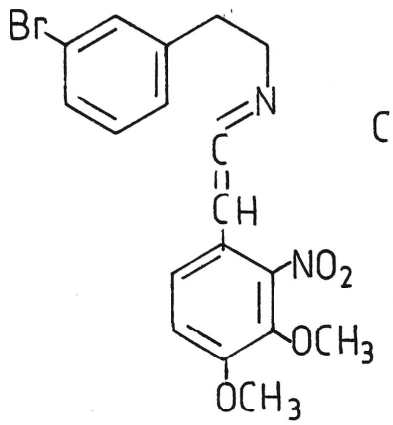

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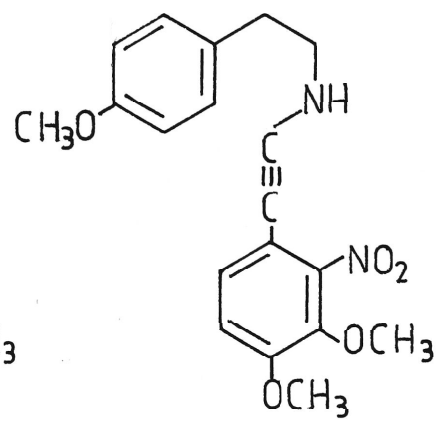
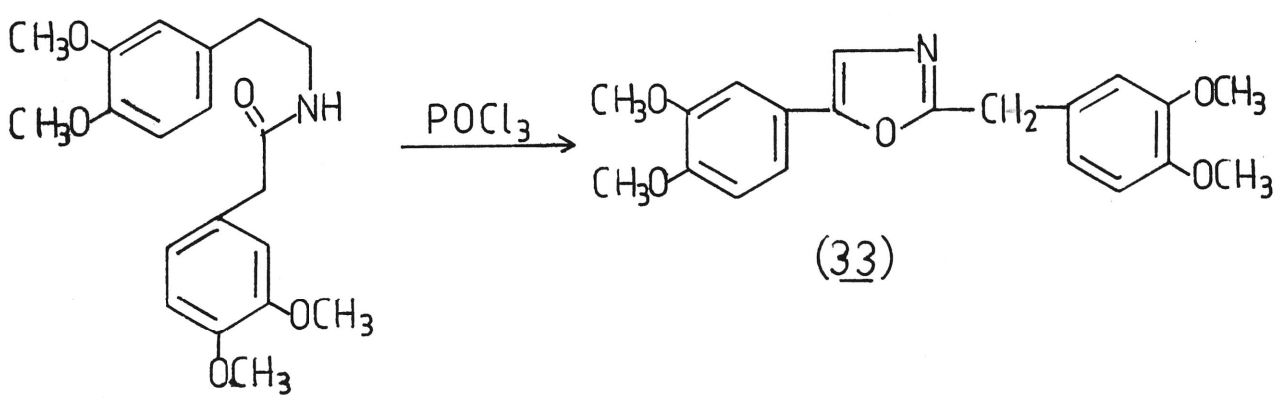


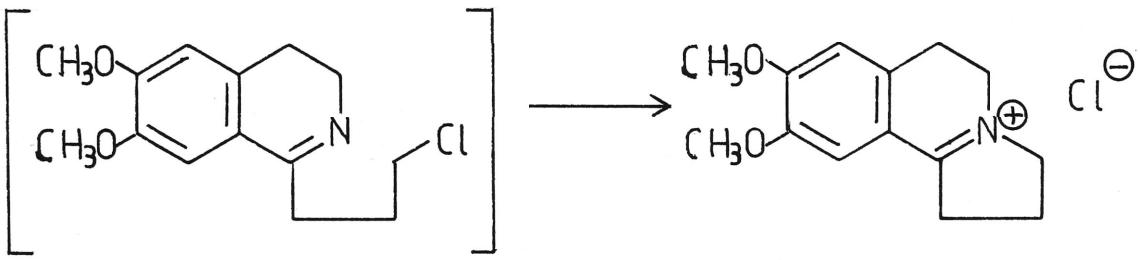
(32)

Attempts to cyclize N-acylphenacylamines gave only oxazoles[62] (33).

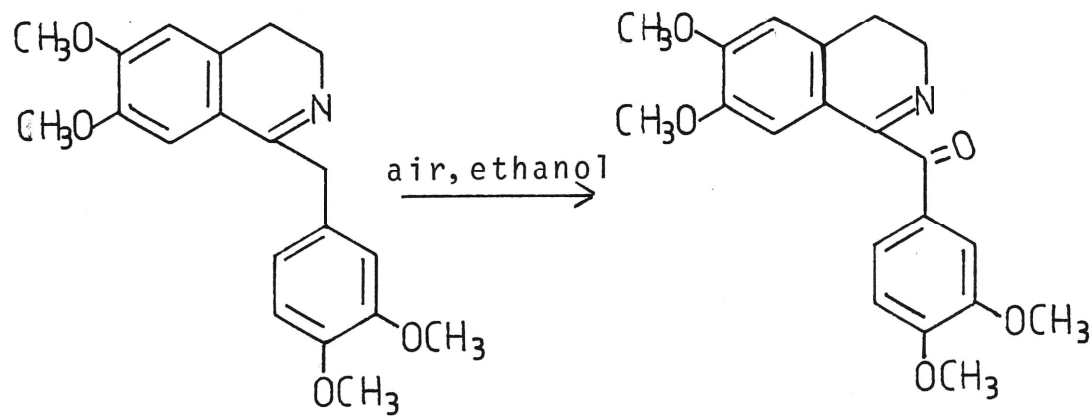


(33)

The substituent in position one of the initially formed isoquinoline ring immediately reacts, intramolecularly, forming compounds with benzoindolizidinium structure. Typical secondary reactions involve γ-chloropropyl group[63].

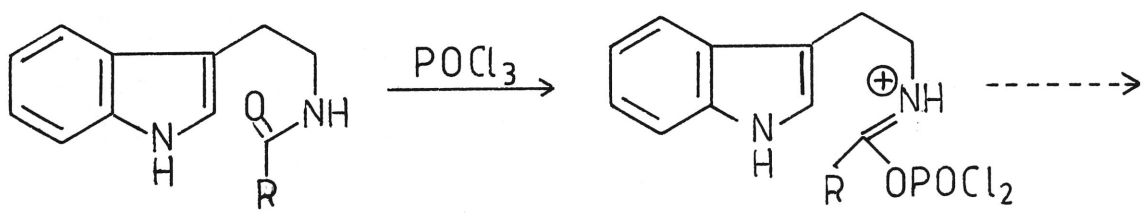


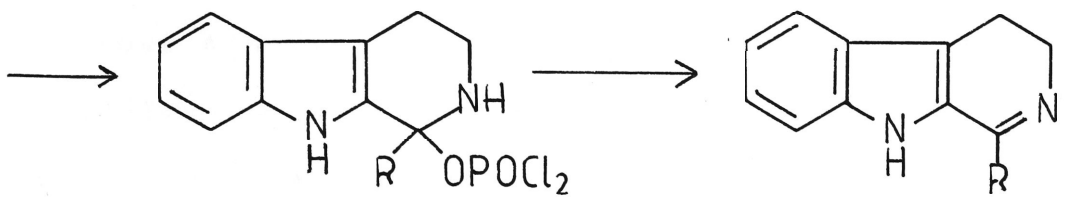
Numerous other substituted 1-benzyl-3,4-dihydroisoquinolines undergo air oxidation to 1-benzoyl-3,4-dihydroisoquinoline[64,65] either in neutral or in alkaline solution. Oxidation, however, does not take place in dilute acid solutions[66].



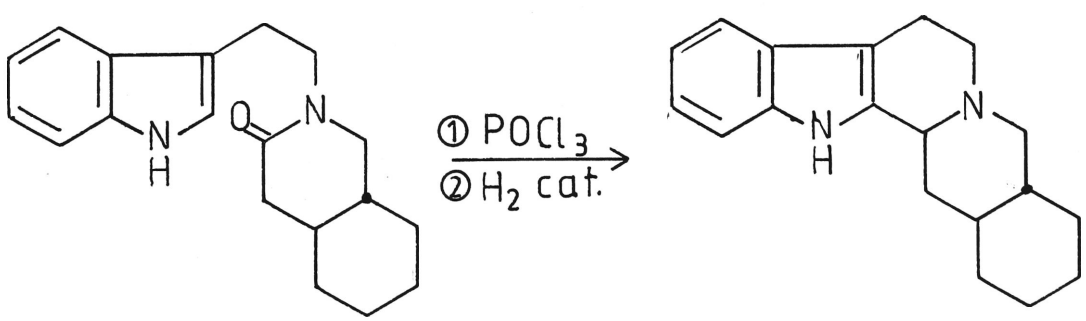
Oxidation by atmospheric oxygen may simultaneously oxidize and dehydrogenate e.g. 1-(o-methylbenzyl)-3,4-dihydro-2-carboline to yobyrone[67]. The changes are, as expected, more rapid in alkaline methanolic solution[68]. A somewhat similar reaction, the cyclization of N-formyl-tryptophan with phosphorus oxychloride at 125°C yielded 36% of norharmane[69]. Finally, N-(β-phenethyl)cyanoacetamide was simultaneously cyclized, hydrolyzed and decarboxylated by phosphoric acid at 170° forming 1-methyl-3,4-dihydroisoquinoline[70].

The ring-closure of N-acylated tryptamines to 3,4-dihydro-β-carbolines is also carried out by the Bischler-Napieralski reaction. Abramovitch[12] in his review tabulated a large number of successful cyclizations which were catalyzed, as they were in the case of isoquinoline formation, by phosphorus pentoxide or by phosphorus oxychloride. The mechanism of the reaction is, as outlined below, practically identical with the one applying to the formation of the isoquinoline ring system.



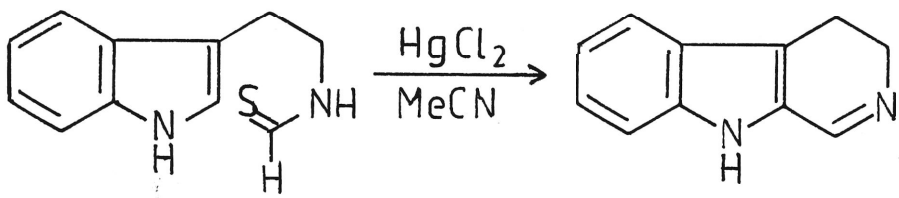


The reaction involves electrophilic attack by the carbonium ion on the indole ring either at the C-2, or more likely at C-3 followed by rearrangement, with subsequent elimination of a mole of water[71]. This reaction proceeds with ease, e.g. N-phenylacetyl-β-(3-indolyl)ethylamine gives, with phosphorus oxychloride, 1-benzyl-3,4-dihydro-β-carbolines[6] in 90% yield. If the starting material used was the formamide derivative the unsubstituted 3,4-dihydro-β-carboline could be obtained in 76% yield at 110° in presence of phosphorus oxychloride[72]. The synthesis of stereoisomeric yohimbanes[73,74] was accomplished also by the Bischler-Napieralski reaction.



Recently, a new chloroform-soluble catalyst, a polyphosphate ester[75] was shown to give yields superior to those achieved by phosphorus pentoxide. Table 1 tabulates the yields of β-carboline derivatives synthesized from acyltryptamines.

Thioacyl tryptamines also cyclize to 3,4-dihydro-β-carboline derivatives in a manner which resembles the Bischler-Napieralski cyclization. Mercuric chloride is used as desulphurizing agent in acetonitrile solution.



The Bischler-Napieralski reaction is expanded to be applicable for the synthesis of more complex compounds, e.g. indoloquinolizidine alkaloids. In this manner a number of such alkaloids were synthesized like the stereoisomeric dihydrocorynantheine[76], ajmalicine[16] and eburnamonine[77] as shown by the example dihydrocorynantheine.

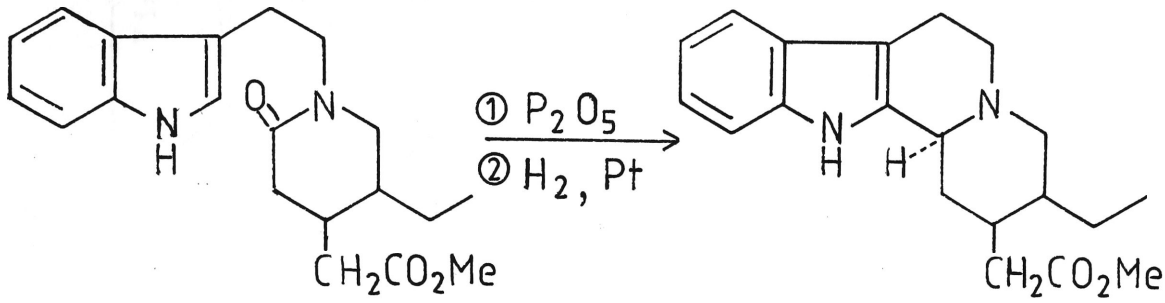

① P_2O_5
② H_2, Pt
N
H
O
N
CH_2CO_2Me
N
H
H
N
CH_2CO_2Me

TABLE I

Bishler-Napieralski Cyclization of Acyltryptamines

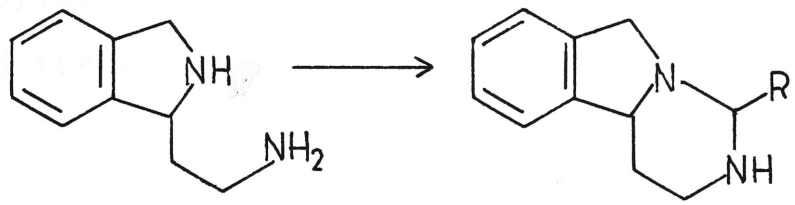
Tryptamine Substituent	Acyl gp.	Cyclization Agent	Yield %
None	Formyl	Polyphosphate ester	73
None	Benzoyl	Polyphosphate ester	68
None	Cyclohexanacetyl	Phosphorous pentoxide	low
None	o-Carboxyphenylacetyl	Phosphorous oxychloride	36
None	o-Methylphenylacetyl	Phosphorous pentoxide	63
α-Carboxy	Formyl	Polyphosphate ester	58

D I S C U S S I O N

A. AIM AND PROPOSED SYNTHESIS

A large number of naturally occurring simple and more complex indole derivatives are known to possess distinct and significant physiological activities. Of these, substituted tryptamine derivatives (some also with additional fused ring systems) affect the human central nervous system. The discovery that some simple isoindole derivatives are also physiologically active resulted in the preparation of a number of relatively simple (and easily synthesizable) isotryptamine derivatives. As findings of this approach showed promise the aim of this investigation became the preparation of new isotryptamine derivatives. These were envisaged to eventually produce fused three-ring-systems, isomeric with - or closely related to - alkaloids of e.g. the harmala group. These products intended to be derivatives of partially saturated isoindolopyrimidine ring systems instead of the β-carboline system of the harmala alkaloids.

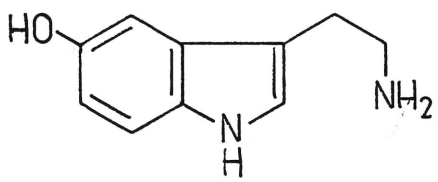
The synthetic programme commenced with the preparation of dihydroisotryptamine (A). Condensation of either the Schiff-bases or the acylated derivatives of dihydroisotryptamine was then envisaged, by modifying either or both the Bischler-Napieralski or the Pictet-Spengler ring closure reactions, to produce the fused isoindolohexahydropyrimidine ring system. While the acylated isotryptamines (acetyl or benzoyl) refused to undergo intramolecular cyclyzation under the conditions used the Schiff bases could be cyclyzed, if reaction conditions used discouraged hydrolysis, to the expected dihydroisoindolo-[1,2-c] hexahydropyrimidine derivatives (B).



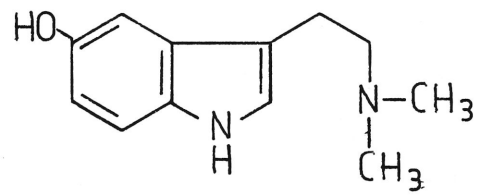
A B

B. DISCUSSION AND RESULTS

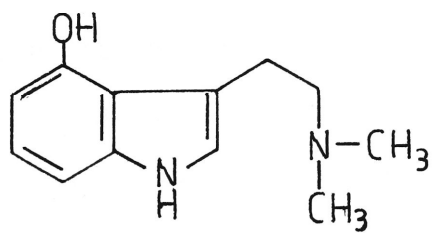
The significant physiological activity of a large number of simple and complete indole derivatives, e.g. serotonine,[78,79] bufotenin,[80] psylocine,[81] lysergic acid diethylamide,[82] reserpine[83] and the *vinca* alkaloids,[84] led to the synthesis of a number of dihydroisoindole derivatives[85] possessing, or failing to possess, physiological activity.



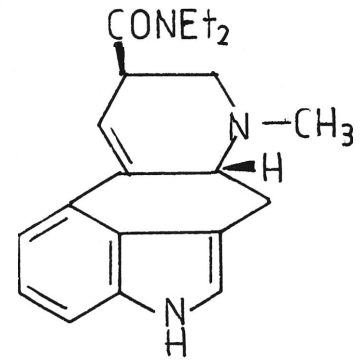
SEROTININE



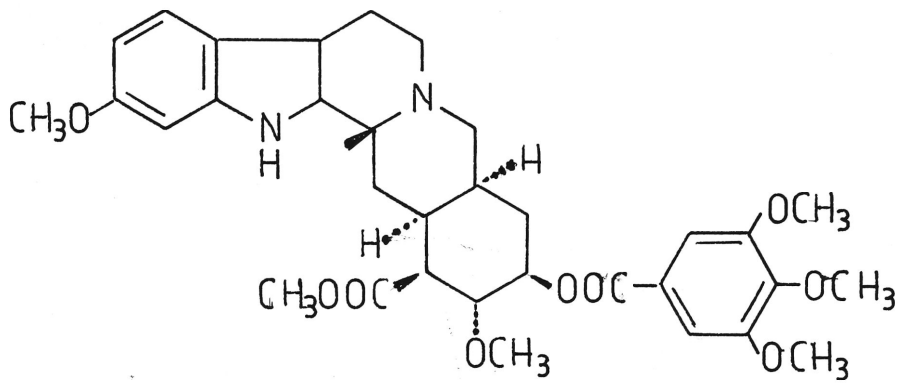
BUFOTENINE



PSILOCYNE

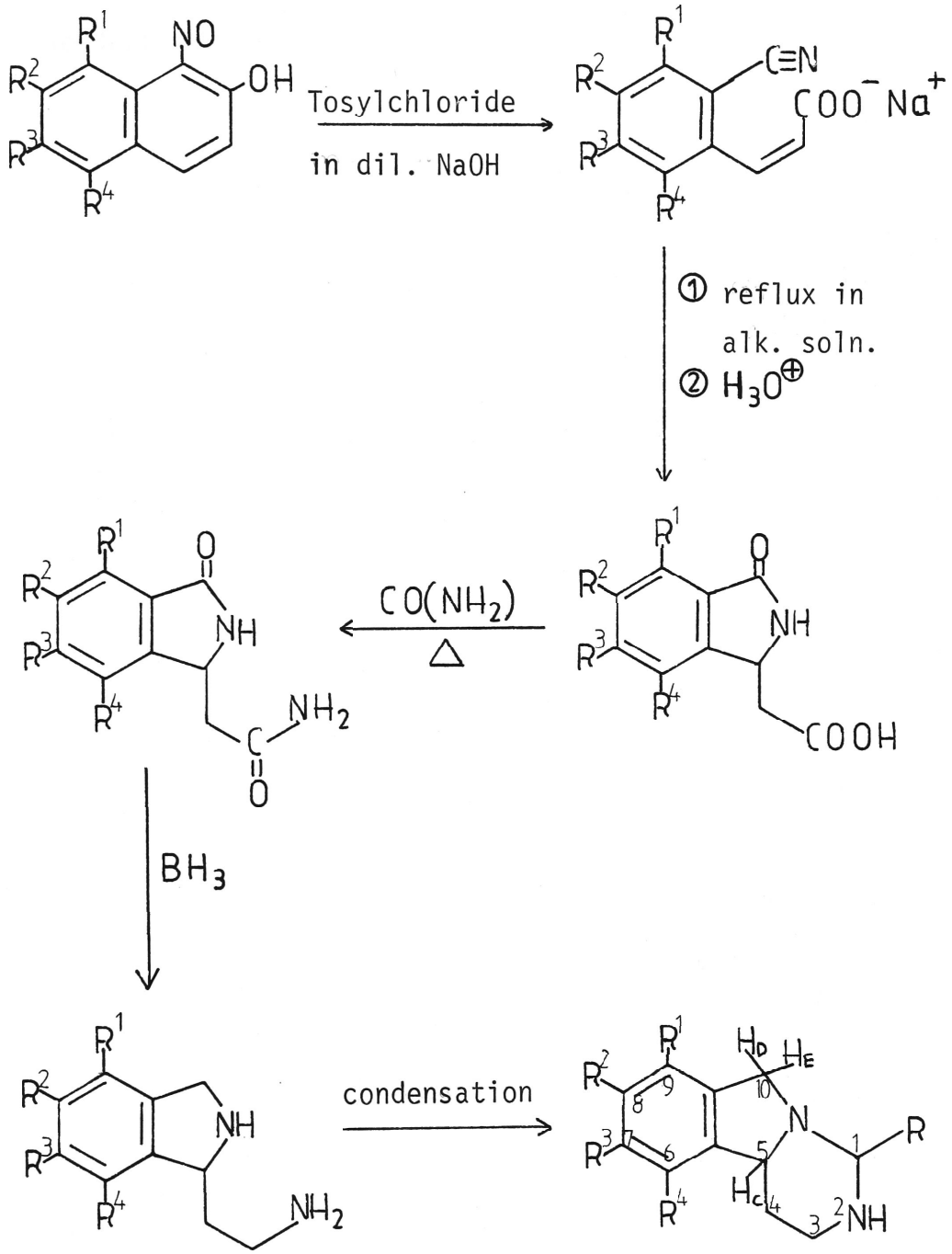


LSD 25



RESERPINE

The methods reported in the literature and utilized for the above syntheses are not conducive to the systematic preparation of such isoindole derivatives. Anyhow, they are not really suitable for synthesis of large enough quantities to enable exploration of their physiological properties. This state of affairs remained as such until the rediscovery of the rearrangement reaction described by Rodionov and Chuckhina[86]. This commences with o-carboxycinnamic acid derivatives and leads to dihydroisoindole-1-one-3-acetic acids. This reaction was then further developed and utilized by Wong[85] for the preparation of dihydroisotryptamine derivatives. The starting material in this thesis was prepared by the above method, but in the form of its hydrochloride.


Tosylchloride
in dil. NaOH
① reflux in alk. soln.
② $H_3O^{\oplus}$
$CO(NH_2)$
$\triangle$
BH_3
condensation

Both the monoacetate and the diacetate of dihydroisotryptamine were prepared by Schotten-Baumann acetylation of the free syrupy base. The monoacetate could not be obtained crystalline but its hydrochloride crystallized well from ethanol. Refluxing either the free base itself or its monoacetate in acetic anhydride for two hours yielded a mixture of the monoacetate, and the diacetate and traces of a third compound which remained unidentified but was not the expected ring-closed derivative. The use of phosphorus oxychloride as a combined dehydrating and intramolecular cyclizing agent was also unsuccessful. The mixture formed in this reaction contained no ring-closed material at all. The benzoyl derivatives were synthesized in the same manner as the acetates. Ring closure was again attempted by warming it gently with phosphorus oxychloride but again no cyclized material could be detected.

The investigation of the Schiff-bases formed from dihydroisotryptamine by reaction with simple aldehydes was, however, more satisfactory. Stirring the base with the appropriate aldehydes at room temperature, usually in chloroform, resulted not only in the formation of the Schiff base (which could not be isolated) but also in simultaneous ring closure. The use of formaldehyde, acetaldehyde and benzaldehyde resulted in the syntheses of the unsubstituted, the 1-methyl and 1-phenyl substituted dihydroisoindolo-[1,2-c]hexahydropyrimidine.

GENERAL

Melting points are uncorrected and were determined on an electrically heated Reichert melting point apparatus.

Silica used for preparative chromatography was "Merck Kieselgel Co. nach Stahl".

Combined organic phases from extractions were dried with anhydrous magnesium sulphate unless otherwise specified.

Mass spectra were recorded on a 21 491-B Double Focus Mass Spectrometer.

Microanalyses were carried out by Amdel Microanalytical Laboratory, Melbourne.

E X P E R I M E N T A L

PREPARATION OF DIHYDROISOTRYPTAMINE

Sodium borohydride (5.7g 149mmole) was suspended in diglyme (75ml) and the solution was added, dropwise, over 24 hours, and under nitrogen atmosphere to a well stirred solution of dihydroisoindole-1-one-3-ethanamide (2.8g, 14.7mmole) dissolved in freshly distilled borontrifluoride/tetrahydrofuran (34.7ml/100ml). The clear yellow solution was then stirred for a further period of 3 days at 30°C to complete the concurrent reduction of both the amide and lactone functions. The excess amount of diborane was destroyed by slow addition of alcohol and the solution was evaporated to dryness in vacuo below 30°C. The amine/borane complex formed was hydrolyzed by standing overnight in 30ml of 0.5N methanolic hydrochloric acid and any borate salt that precipitated was filtered off. The filtrate was evaporated to dryness in vacuo then suspended in dilute aqueous alkali. Any unreacted amide was extracted into dichloromethane. The free amine was obtained from the aqueous alkaline solution by repeated extractions with chloroform. The combined organic phase was dried, filtered, then concentrated under nitrogen, to yield the free amine in form of a viscous oil. This was then chromatographed on a silica column. Elution of the column with ammonium hydroxide/ methanol/chloroform (6/2/3) gave 1.69g (70.7%) of dihydroisotryptamine. Mass spec. (c.i.) m/z 163 (MH^+). The hygroscopic tartrate salt, m.p. 132° was prepared by refluxing stoichiometric quantities of the base and tartaric acid for 15 minutes, then allowing the solution to stand until completed crystallization. The hydrochloride salt was prepared by

passing hydrochloric acid gas into an ethanolic solution of the base for c. 15 minutes, then diluting the solution either with tetrahydrofuran or ethyl acetate. The pure crystals, m.p. 264-266°C, precipitated on standing.

Found: C, 51.0; H, 6.7; N, 12.0;

$C_{10}H_{16}N_2Cl_2$ requires C, 51.1; H, 6.9; N, 11.9%.

Its n.m.r. spectrum (CD_3OD) is identical with that of the free base.

ACYLATION OF DIHYDROISOTRYPTAMINE

(a) Acetylation.

Excess acetic anhydride was added dropwise to a well-stirred solution of dihydroisotryptamine (2.0g) in chloroform (50ml); stirring then continued for another 15 minutes to complete the reaction. The chloroform solution was extracted several times with 0.5N hydrochloric acid until all unchanged starting material and all the basic monoacetate was extracted (Solution A) from the chloroform solution (Solution B). The aqueous acidic solution (A) was basified with 4N sodium hydroxide and extracted exhaustively with chloroform. The chloroform solution was washed with water, dried and passed through an alumina column to separate unchanged starting material. The main product, monoacetyldihydroisotryptamine, was isolated as a viscous oil (1.05g) on evaporation of the chloroform solution. Its hydrochloride salt was prepared by passing dry hydrochloric acid gas into an ethanol/

tetrohydrofuran solution of the basic monoacetate and recrystallizing the product from ethanol M.p. 199-200°C. Mass spectrum (c.i.) m/z 205 (MH^+).

Found:	C, 55.7; H, 7.3; N, 10.8; Cl, 13.7%
Calculated for $C_{12}H_{16}N_2O.HCl.H_2O$	C, 56.0; H, 7.0; N, 11.1; Cl, 13.8%

The chloroform solution (B) was washed with water, then dried and evaporated to yield the N,N'-diacetyldihydroisotryptamine (1.2g). It was recrystallized from ethanol to melt at 140-141°C. Mass spectrum (c.i.) m/z 247 (MH^+).

Found:	C, 68.0; H, 7.1; H, 11.6%
Calculated for $C_{14}H_{18}N_2O_2$	C, 68.3; H, 7.3; N, 11.4%

(b) Benzoylation.

Excess benzoyl chloride (3.8g) was added to a solution of dihydroisotryptamine (2.0g) in chloroform (20ml) and the solution was stirred for one hour at room temperature. The chloroform solution was extracted exhaustively with 0.5N hydrochloric acid (Solution C) to remove unchanged starting material and the basic monobenzoate from the chloroform (Solution D).

The aqueous acidic solution (C) was basified with 4N sodium hydroxide solution and extracted with chloroform.

The combined chloroform solution was washed with water, dried, then passed through an alumina column to separate unchanged starting material. Evaporation of the chloroform solution gave the basic monobenzoyldihydroisotryptamine (1.2g) as a viscous oil. The oxalic acid salt of the base was prepared by adding a saturated oxalic solution in ethanol to a saturated ethanolic solution of the basic monobenzoate and recrystallizing the precipitate from alcohol, m.p. 98-99°C. Mass spectrum (c.i.) m/z 267 (MH^+).

Found:	C, 61.2; H, 5.8; N, 7.5%
Calculated for $C_{17}H_{18}N_2O.(COOH)_2.H_2O$	C, 61.0; H, 5.9; N, 7.5%.

The chloroform solution (D) was washed with water, dried, chromatographed on an alumina column, then evaporated to dryness to give N,N'-dibenzoyldihydroisotryptamine. as a colourless syrup. Mass spectrum (c.i.) m/z 371 (MH^+).

(C) Acetylation by an Alternate Method.

Excess acetyl chloride was added dropwise to a well-stirred solution of dihydroisotryptamine in chloroform at room temperature and allowed to stand for a further 15 minutes to complete the reaction. Application of the technique used above, when acetic anhydride was the reagent selected, produced the same mono- and di-acetyl

derivatives in comparable yields.

ATTEMPTS TO CYCLYZE THE MONOACYLATED COMPOUNDS

(a) Monoacetyldihydroisotryptamine (1.0g) was refluxed with phosphorus oxychloride (23.4g) in chloroform (100ml) for 20 minutes, then cooled to room temperature. Sodium hydroxide (4N) was then added to neutralize the acids and to extract them from the chloroform solution. The chloroform solution, which remained after the extraction, was washed with water, dried, and evaporated to dryness. The residue was extracted with ethanol and the soluble material was investigated in the mass spectrometer. This showed the presence of only the starting material and some desacetylated compound in the reaction mixture. No trace of any cyclyzed compound could be found.

(b) Monoacetyldihydroisotryptamine (1.0g) was refluxed in acetic anhydride (20ml) for 2 hours. After cooling to room temperature the reaction mixture was basified and extracted with chloroform. The combined chloroform extract was washed with water, dried, and evaporated to dryness. Mass spectroscopic investigation of the residue revealed the presence of only the mono- and diacetates in the reaction mixture. No trace of cyclyzed material could be detected.

(c) Monobenzoyldihydroisotryptamine (1.0g) was refluxed as for monoacetyldihydroisotryptamine (cf. (a) with) phosphorus oxychloride (23.4g) in chloroform (100ml) for

20 minutes. Mass spectral examination of the reaction mixture formed again revealed the presence of only the monobenzoate and some debenzoylated material. No trace of any cyclyzed compound could be found.

PREPARATION OF DIHYDROISOINDOLO-[1,2-c]HEXAHYDROPYRIMIDINES

(a) Formalin (0.75ml) was added to a stirred solution of dihydroisotryptamine (2.0g) dissolved in dry tetrahydrofuran or ethanol. The mixture was stirred at 25°C for 2 days, when the solvent was evaporated. The red oil was suspended in 2N sodium hydroxide solution and extracted into chloroform. The chloroform solution was chromatographed on alumina using chloroform/methanol/conc. ammonia (75:90:1) mixture as eluant. The viscous oil showed m/z 175 (MH^+) in the mass spectrum.

Found: C, 75.9; H, 8.2; N, 15.9%

Calculated for $C_{11}H_{14}N_2$: C, 75.8; H, 8.1; N, 16.1%.

Its oxalic acid salt was prepared by adding a saturated oxalic acid solution to a saturated ethanolic solution of the above base and recrystallizing the precipitate from alcohol. M.p. 160-161°.

(b) Acetaldehyde (0.4g) was added to dihydroisotryptamine (2.0g) dissolved in anhydrous ethanol (18ml) under nitrogen atmosphere for one hour. After an hour's stirring, the reaction was complete (TLC) and the solvent

removed in vacuo. The crude base which precipitated was taken into chloroform and chromatographed on alumina using a chloroform/methanol/conc. ammonia mixture as the eluant. Evaporation of the chloroform yielded a viscous oil. Mass spectrum (c.i.) m/z 189 (MH^+). Its oxalic acid salt was prepared as the one formed with formaldehyde. The salt was then recrystallized from alcohol. M.p. 197-198°C.

Found: C, 64.2; H, 7.3; N, 11.5%

Calculated for $C_{12}H_{16}N_2.\frac{1}{2}(COOH)_2.\frac{1}{2}H_2O$: C, 64.4; H, 7.4; N, 11.6%

(c) Benzaldehyde (1.0g) was added dropwise to dihydroisotryptamine (2.0g) dissolved in anhydrous ethanol under a nitrogen atmosphere. After refluxing the mixture for 5 minutes, the solid formed was evaporated to dryness in vacuo, and was washed with water to remove any water-soluble impurities present. The purified solid produced was recrystallized from ethanol yielding colourless crystals of 1-phenyldihydroisoindolo-[1,2-c]hexahydropyrimidine, m.p. 105-106°C. Mass spectrum (c.i. m/z 251 (MH^+).

Found: C, 78.6; H, 7.4; N, 11.1%

Calculated for $C_{17}H_{18}N_2.\frac{1}{2}H_2O$: C, 78.8; H, 7.3; N, 10.8%.

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